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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/754,547 | 01/12/2004 | Longgui Wang | 15741.004 | 9273 |
| <div>7590 FENNEMORE CRAIG Suite 2600 3003 N. Central Avenue Phoenix, AZ 85012</div> | | | <div>EXAMINER JAGOE, DONNA A</div> | |
| | | | <div>ART UNIT 1614</div> | <div>PAPER NUMBER</div> |
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

| | | | |
|------------------------------|--------------------------------------|------------------------------------|--|
| Office Action Summary | Application No. 10/754,547 | Applicant(s) WANG ET AL. | |
| | Examiner Donna Jagoe | Art Unit 1614 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 18 January 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-11, 13, 14 and 17-30 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-11, 13, 14 and 17-30 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>8/15/07, 1/16/08, 1/29/08</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicants' arguments filed January 16, 2008 have been fully considered and they are deemed to be persuasive regarding previous rejections of record. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

However, upon reconsideration, the following rejections and/or objections are newly applied. They constitute the complete set presently being applied to the instant application.

Claims 1-11, 13, 14 and 17-30 are pending in this application.

Regarding the election of a single disclosed species, Meisoindigo, Formula IV, the species was not specifically found for the purpose of treatment of inflammation, however, the search was extended to include the other active agents of the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 13 recites the limitation "the method according to claim 1, wherein the neurodegenerative disorder is ..." in lines 1-2 of the claim. There is insufficient

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antecedent basis for this limitation in the claim because there is not a neurodegenerative disorder recited in instant claim 1 from which claim 13 depends.

Claim 14 is indefinite to the extent that it reads on the rejected base claim.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-11, 17-19, 21, 23 and 25-30 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11, 13, 14, 16-24 and 29-32 of copending Application No. 11/494362. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant and conflicting claims recite substantially the same subject matter, differing only in the description of the particular components claimed. For instance,

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conflicting claim 1 requires method of treating inflammatory arthritis comprising administering inter alia, meisoindigo.

None of the instant claims recites specifically inflammatory arthritis, but conflicting claims 1-11, 13, 14, 16-24 and 29-32 are fully encompassed by the instant claims because they are drawn to a method of treatment of inflammatory arthritis. Since inflammatory arthritis is an inflammatory disorder such as those instantly claimed it would have been obvious to anyone of ordinary skill in the art that the claims overlapped in scope in this manner. Further, using applicants' instant specification as a dictionary to determine the meaning of a term in the patent claim, the examiner turns to, for example page 4, wherein rheumatoid arthritis is cited as an example of a chronic inflammatory disease. One skilled in the art would have been motivated to have interpreted the claims as broadly as is reasonable, and in doing so recognize that they are coextensive in scope and thus the proper subject of an obviousness-type double patenting rejection as outlined by *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 2, 4, 5, 7-11, 14, 17-24 and 26-30 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 10-18, 20, 21 and 24-36 of copending Application No. 11/104422. Although the conflicting claims are not identical, they are not patentably distinct from each other

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because the instant and conflicting claims recite substantially the same subject matter, differing only in the recitation of the cytokine expression levels in conflicting claim 1. Conflicting claims 10-18, 20, 21 and 24-36 are fully encompassed by the instant claims because they are drawn to a method of treatment of inflammatory related disease. One skilled in the art would have been motivated to have interpreted the claims as broadly as is reasonable, and in doing so recognize that they are coextensive in scope and thus the proper subject of an obviousness-type double patenting rejection as outlined by *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

New Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 5, 7-11, 13, 14, 19-21 and 24-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eisenbrand et al. WO 00/61555 in view of Alternative Medicine Review (2002) and in further view of Drug Facts and Comparisons (1994).

Eisenbrand et al. teach indirubin (reads on formula III of instant claim 1), indigo and isoindigo (each reads on formula II of instant claim 1) are natural products which can be obtained from different plants, including *Isatis tinctoria*. Indigo naturalis is reported to have inter alia anti-inflammatory activity (page 1, lines 4-21). Eisenbrand et al. Alternative Medicine Review teaches that *Isatis tinctoria* is strongly inhibitory to the cyclooxygenase-2 enzyme and is theorized to be largely responsible for the anti-inflammatory action of *Isatis* (page 523). Inflammatory conditions are considered a major indication for *Isatis* leaf (page 524).

Both references identify the common problem of treating *Inflammation* with plants that contain indirubin and teaches that they have been well known to treat inflammatory conditions. Eisenbrand et al. gives specific example of a plant that carries indirubin, an

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isomer of indigo; the plant *Isatis tinctoria*, and Alternative Medicine Review teaches that *Isatis tinctoria* is a COX-2 inhibitor and is indicated for treatment of inflammatory conditions. It is therefore reasonable to conclude that the strength of correlation between references gives rise to reasonable expectation of success from combining them.

Regarding the combination of an analgesic/anti-inflammatory agent with the indirubin derivatives, Drug Facts and Comparisons teach analgesic agents (page 1210) such as ibuprofen and indomethacin are NSAIDs and routinely employed in the treatment of inflammatory diseases, such as rheumatoid arthritis (see chart, page 1211). As stated in *In re Kerkhoven*, 626 F.2d 846, 205 USPQ 1069, at page 1072 (CCPA 1980):

It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose. *In re Susi*, 58 CCPA 1074, 1079-80, 440 F.2d 442, 445, 169 USPQ 423, 426 (1971); *In re Crockett*, 47 CCPA 1018, 1020-21, 279 F.2d 274, 276-77, 126 USPQ 186, 188 (CCPA 1960). As this court explained in *Crockett*, the idea of combining them flows logically from their having been individually taught in the prior art.

While the recited inflammatory conditions are not specifically recited, it is prima facie obviousness to select a known material based on its suitability for its intended use, inflammation as recited by Alternative Medicine Review. See *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945). Also, established precedent holds that it is generally obvious to add known ingredients to known compositions with the expectation of obtaining their known function. See, e.g., *In re Linder*, 457 F.2d 506, 507 (CCPA 1972); see also *In re Dial*, 326 F.2d 430,432 (CCPA 1964). Since the

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instantly claimed conditions such as inflammatory bowel disease and Crohn's disease are inflammatory conditions, it would have been obvious to employ the anti-inflammatory indirubin derivatives optionally combined with the instantly claimed well known anti-inflammatory agents because they are known to possess anti-inflammatory characteristics in the compositions of the primary reference.

Claims 1-11, 13, 14 and 17-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kunikata et al (C3 from IDS dated August 15, 2005), Kabushiki Kaisha Hayashibara Seibutsu Kagaku Kenyujo EP 0 987 027 A1 (B1 from IDS dated August 15, 2005) and Drug Facts and Comparisons (1994) and in further view of Liu (C47 from IDS dated January 16, 2008).

Kunikata et al. teach *Polygonum tinctorium* is known to have the ability to suppress inflammation. The compounds indirubin (reads on formula II) and indigo (reads on formula I) were isolated from *P. tinctorium* and exert an inhibitory effect on interferon- γ , which is a well-known inflammatory cytokine and also inhibits interleukin-6 (IL-6) production (see abstract). Kunikata states that the so-called inflammatory cytokines are induced in response to inflammatory stimuli. These inflammatory cytokines accelerate inflammatory reactions through activation of immunocompetent cells. Interferon γ , recited above, is thought to be a member of the inflammatory cytokine family (page 93, column 1 bridging to column 2). Kunikata isolated the active compounds indirubin and indigo (fig. 2, page 95) from *P. tinctorium* based on their ability

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to inhibit interferon- γ production (page 93 column 2). When tested it inhibited production of interleukin-6 in murine splenocytes (page 96, column 2).

Kunikata does not teach co-administration of other anti-inflammatory agents.

Kabushiki Kaisha Hayashibara Seibutsu Kagaku Kenyujo (hereinafter referred to as "Kabushiki") teaches physiologically active extract of an indigo plant (see abstract) which exhibits anti-inflammatory effects (page 2 paragraph 0011). It is noted that the properties include controlling the production of cytokines including interferon- γ and interleukin 10 by immunocompetent cells. Treatment of conditions such as digestive diseases, Crohn's disease, Idiopathic ulcerative colitis, inflammation of pulmonary alveoli, multiple sclerosis, Alzheimer's disease, etc. are recited on pages 5-6 paragraph 0023. It does not teach the concomitant administration of another anti-inflammatory agent.

Drug Facts and Comparisons teach analgesic agents (page 1210) such as ibuprofen and indomethacin are NSAIDs and routinely employed in the treatment of inflammatory diseases, such as rheumatoid arthritis (see chart, page 1211). One of ordinary skill in the art of the references listed above would have been a medical doctor with pharmaceutical or clinical research experience, or a chemist, biochemist, or a pharmacologist with a doctoral degree and with experience in the pharmaceutical industry, and either of which would also have had ability in identifying appropriate and acceptable combinations of active ingredients for commercial medications for symptoms of inflammation.

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It would have been obvious to one having ordinary skill in the art to combine the anti-inflammatory agents indigo and indirubin as noted in Kunikata et al. and Kabushiki as noted above with anti inflammatory agents NSAIDs such as ibuprofen and indomethacin as noted in Drug Facts and Comparisons to treat inflammatory conditions, such as arthritis or inflammatory bowel disease with the reasoned expectation that it would reduce inflammation and the markers of inflammation, such as interleukin 6 and 10 as recited in Kunikata et al. and Kabushiki respectively. The combination of any of indirubin and indigo with any of the NSAIDs instantly claimed would have performed the same function as it did separately. One of ordinary skill in the art would have recognized that the results of the combination were predictable at the time the invention was made. The nature of the problem to be solved, treatment of inflammatory arthritis, as well as the need to increase efficacy of the overall treatment of inflammatory disease would have led one of ordinary skill in the art to combine the indigo derivatives of Kunikata and Kabushiki together with the NSAIDs of Drug Facts and Comparisons. Therefore, it would have been obvious to treat inflammatory arthritis with indigo and indirubin combined with NSAIDs.

Regarding instant claim 3 and 22 drawn to an increase in solubility of the compound when at least R1 or R2 is in a group that increases solubility, Liu et al. teach that indirubin has poor solubility, poor absorption and irritation of the gastrointestinal tract and methylisoindigotin, abbreviated as meisoindigo (formula IV), a second generation derivative of indirubin exhibited higher activity than indirubin and less toxicity. The higher activity would indicate that the meisoindigo has a higher solubility

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over indirubin. Express suggestion to substitute one equivalent for another need not be present to render such substitution obvious.

Regarding the administration of the indigo derivatives for inflammatory-related disease associated with cytokine expression levels, it would have been obvious to employ the recited indirubin and indigo compositions motivated by the teaching of Kunikata et al. and Kabushiki that indirubin and indigo exert anti-inflammatory, alleviation and detoxification actions (Kabushiki page 2 paragraph 11) by controlling the production of cytokines including interferon- γ and interleukin 10 by immunocompetent cells which relate to the determination of the balance between type 1 helper T-cells (Th1) and type 2 helper T-cells (Th2) to control the balance within the normal conditions and to treat/prevent the diseases such as autoimmune diseases (Kabushiki page 3, paragraph 0016). Inflammatory arthritis is an inflammatory related disease associated with cytokine levels.

Regarding claims 8 and 25, drawn to administration of at least two compounds administered concurrently or sequentially, the nature of the problem to be solved, treatment of inflammatory arthritis with an indigo derivative, would have led one of ordinary skill in the art to choose an appropriate carrier for the combination of two indigo derivatives to treat the symptoms of inflammatory arthritis administered together or in sequence. It would have been obvious to use a combination two indigo derivatives to lower toxicities by combining an optimal formulation of the indigo derivatives.

Since the instantly claimed conditions such as inflammatory bowel disease and Crohn's disease are inflammatory conditions, it would have been obvious to employ the

anti-inflammatory indirubin derivatives optionally combined with the instantly claimed well known anti-inflammatory agents because they are known to possess anti-inflammatory characteristics in the compositions of the primary reference.

Response to Arguments

Applicant's arguments with respect to claims 1-11, 13, 14 and 17-30 have been considered but are moot in view of the new ground(s) of rejection.

Applicant indicates that a clear line of demarcation will be maintained in view of claims 10-36 of Application No. 11/104,422 and with regard to Application No. 11/494/362, a terminal disclaimer upon allowance of the claims will be filed, if necessary.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna Jagoe whose telephone number is (571) 272-0576. The examiner can normally be reached on Monday through Friday from 8:00 A.M. - 4:30 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Donna Jagoe /D. J./
Examiner
Art Unit 1614

April 23, 2008

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614